Clinical Studies of Thiazide-Induced Hyponatremia

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To determine the prevalence and vulnerability of symptoms from thiazide-induced hyponatremia, we reviewed 223 cases of symptomatic hyponatremia enrolled between January 1996 and April 2002. There was a high frequency of neurologic manifestation of thiazide-induced hyponatremia, whereas clinical dehydration was not a discernible feature. Female patients presented with lower serum sodium levels than male counterparts (114 ± 8 versus 117 ± 8 mmol/L, P=0.02), although the frequency of central nervous system manifestation was comparable between two gender groups. The most frequent symptoms were malaise and lethargy (49%), followed by dizzy spells (47%) and vomiting (35%). Degree of hyponatremia upon presentation predicted the development of confusion and vomiting symptoms. Serum sodium concentration ≤115 mmol/L was significantly associated with the development of confusion (odds ratio 2.6, 95% confidence interval 1.3 to 5.1, P=0.004). Our results show that symptoms from thiazide-induced hyponatremia primarily reflect osmotic water shift into brain cells rather than extracellular fluid volume depletion.

Key words: hyponatremia ■ thiazide ■ symptoms

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INTRODUCTION

Thiazide diuretic-induced hyponatremia is a common cause of symptomatic hyponatremic disorders.[1] To establish the diagnosis of thiazide-induced hyponatremia, we need simple biochemical investigation. Nonetheless, delayed diagnosis of this disease entity commonly occurs because of overlooking the vague presentation of thiazide-induced hyponatremia. Symptomatology of this subgroup of hyponatremic disorder deserves specific consideration because: 1) delayed recognition of this potentially preventable disease would lead to mortality and morbidity, and 2) symptom analysis aids in understanding of the pathophysiology. To evaluate the symptoms of thiazide-induced hyponatremia, we undertook a survey to determine the frequency of such symptoms and the corresponding risk factors.

METHODS

Subjects

A total of 223 patients with thiazide-induced hyponatremia were identified over six years of study period (between January 1996 and April 2002). We only included those clinically significant hyponatremia episodes which were symptomatic, necessitating hospitalization with a serum sodium level below 130 mmol/L. The baseline characteristics of the patients recruited have been reported elsewhere.[2] As described before, the diagnosis of thiazide-induced hyponatremia is based on a history of diuretic use and the finding that hyponatremia resolved after discontinuing the offending agent in the absence of other specific therapies for hyponatremia.[3] Clinical manifestation, health status, and covariates were ascertained by case records review, supplemented by telephone interviews if indicated.

Statistical Analysis

Analyses were performed by Statistical Package for the Social Sciences for Windows software, version 11.0 (SPSS Inc., Chicago, IL). Categorical vari-

ables were analyzed with the use of Chi-squared test or, when appropriate, Fisher's exact test. Continuous variables were analyzed with the use of Student's *t* test; the results are expressed in mean ± standard deviation (SD) unless otherwise specified. Odds ratios and 95% confidence intervals were calculated. A P value of below 0.05 was considered significant. All probabilities were two-tailed.

RESULTS

Among 223 consecutive patients diagnosed with thiazide-induced hyponatremia, mean serum sodium concentration measured 116 mmol/L (range 98 to 128 mmol/L). The mean age and body mass index of these patients were 76 ± 9 years and 22.4 ± 3.7 kg/m^2, respectively. Seventy percent of the cases were females who presented with lower serum sodium levels than male counterparts (114 ± 8 versus 117 ± 8 mmol/L, P=0.02) (Figure 1). There was otherwise no significant difference in demographic and clinical characteristics between the two gender groups (Table 1). Overall, baseline creatinine clearance, as estimated by Cockcroft-Gault equation,[4] was 47 ± 22 ml/minute. During hyponatremic episodes, mean urinary osmolality measured 392 ± 159 mOsm/kg as compared with serum osmolality of 238 ± 18 mOsm/kg, reflecting impaired diluting ability of urine. Clinical dehydration was evident in only 24% of the cases. During the onset of thiazide-induced hyponatremia, the mean serum urea: creatinine ratio was 1:14, and serum bicarbonate level being 26 ± 5 mmol/L. Mean systolic and diastolic blood pressures were 151 ± 25 mmHg and 77 ± 14 mmHg, respectively. The serum uric acid level was 0.31 ± 0.16 mmol/L, and serum potassium concentration was 3.3 ± 0.8 mmol/L.

Thiazide-induced hyponatremia commonly caused neurologic manifestation (Table 2), which led to the performance of brain computed tomography in 47 out of the 223 patients. The most frequent symptoms were malaise and lethargy, as encountered in almost half of the cases. Forty-seven percent of the cases in our series reported dizzy spells. Other important symptoms included vomiting (35%) and mental confusion or obtundation (17%). Seventeen percent of patients presented with falls prior to the diagnosis of thiazide-induced hyponatremia. In particular, degree of hyponatremia upon presentation predicted the development of confusion (Figure 2) and vomiting symptoms (Figure 3). For instance, mean serum sodium concentration among confused patients was significantly lower than subjects without mental disturbance (111 ± 8 versus 117 ± 8 mmol/L, P<0.001). By univariate analysis, serum sodium concentration ≤115 mmol/L was significantly associated with the development of confusion (odds ratio 2.6, 95% confidence interval 1.3 to 5.1, P=0.004) and vomiting (odds ratio 1.8, 95% confidence interval 1.1 to 3.1, P=0.02). Serum potassium levels and duration of thiazide diuretics, on the other hand, had no discernible correlation with these symptoms, including presence of vomiting.

In terms of individual susceptibility to develop symptoms with hyponatremia, patient age did not predict the occurrence of falls with hyponatremia (P=0.73). There was comparable frequency of central

Table 1. Baseline Characteristics of Male and Female Subjects

	Female Group (n=157)	Male Group (n=66)	P Value
Age (years)	77 ± 8	76 ± 9	0.06
Body mass index (kg/m^2)	22.4 ± 3.9	22.6 ± 3.0	0.69
Institutionalization	25 (16%)	8 (12%)	0.32
Ability to walk			
Entirely independent	96	45	
Independently with assistive device	45	14	
Help from another or chair bound	12	4	0.47
Unknown	4	3	
Duration of thiazide use (days)†			
	118 (25–757)	66 (9–309)	0.36
Diabetes mellitus	40 (25%)	15 (23%)	0.40
Use of nonsteroidal anti-inflammatory drugs	24 (15%)	10 (15%)	0.29

* Plus-minus values are mean ± SD unless otherwise indicated; † Median (IQR) days.

nervous system manifestation in male and female patients (details not shown), despite a lower serum sodium level in the latter group as described above.

Two cases developed seizures, and three required intensive care unit admission. However, none of the 223 cases had noncardiogenic pulmonary edema or coma. All patients improved after discontinuation of thiazide, but 14 of them had recurrence of hyponatremia after resuming thiazide diuretics. One additional patient subsequently exhibited clinical and radiologic manifestation of osmotic demyelination syndrome or central pontine myelinolysis. No mortality occurred in our cohort. Median hospitalization duration was five days.

DISCUSSION

Intriguingly, thiazide-induced hyponatremia patients do not fit well into usual classifications of sodium disorder because of their ambiguous volume status. As illustrated in our case series and supported by previous observation,[5-7] most of them appear clinically euvolemic or even with volume expansion in spite of sodium and potassium depletion. The finding of impaired diluting ability in our series comes as no surprise, because thiazide diuretics stimulate antidiuretic hormone (ADH) release, inhibit electrolyte transport at the cortical diluting sites, and increase fractional proximal water reabsorption.[6] Nonetheless, evidence for positive water balance in thiazide-induced hyponatremia has thus far remained controversial despite the presence of volume expansion (as suggested by the relatively low uric acid level and normal serum urea: creatinine ratio, for instance) in the majority of cases here.

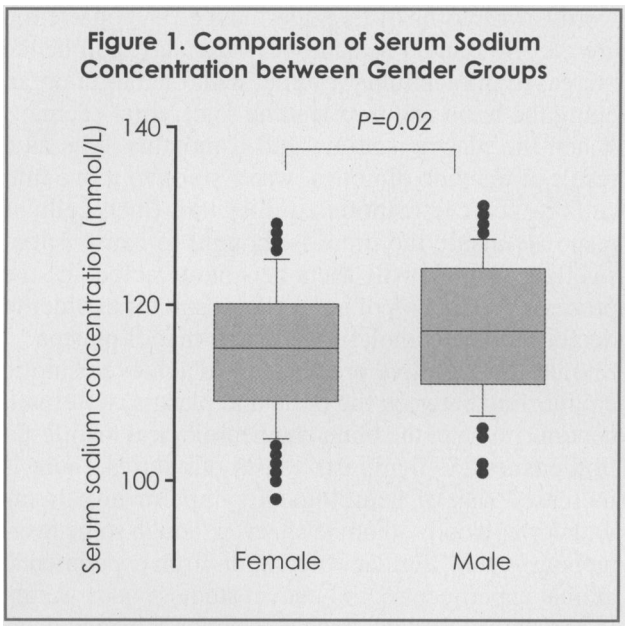
Our observation further confirmed that the manifestations are primarily central nervous system in origin, with their severity partly reflected by the absolute decrease in plasma sodium concentration. In other words, symptoms of thiazide-induced hyponatremia are closely related to osmotic water shift and hence increased intracellular volume, with the target organ being the brain and thus leading to cerebral edema.[8,9] When the plasma sodium and osmolality falls as a result of thiazide diuretics, water starts to move into cells to achieve osmotic equilibrium. Such cellular response inside the brain is thought to cause initial swelling, which will then be counteracted by the process of extrusion of intracellular solutes in order to decrease brain osmolality to match that of plasma.[9-11] Should this adaptive process fail to achieve osmotic equilibrium between the brain and plasma, water will continue to enter the brain and neurological manifestation ensues. As demonstrated in our series, there is increased risk of neurological symptom in patients with lower blood sodium level, even though some overlapping occurs. Similar observation from experimental animal experiments[12] and human studies[13] adds weight to our clinical finding. Such association is also biologically plausible because water influx into the brain is expected to be driven by the degree of plasma osmolality. The overlap of sodium levels, on the other hand, emphasizes how complex and multiple the pathogenesis of thiazide-induced hyponatremia symptom could be. Of note, the link between the rate of serum sodium fall and neurological symptom propensity could not be addressed in our retrospective analysis.

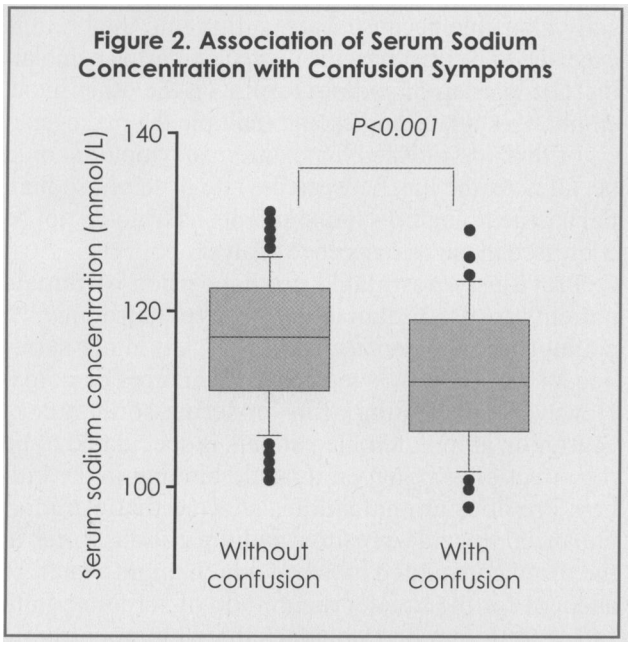
Table 2. Symptoms of Thiazide-Induced Hyponatremia

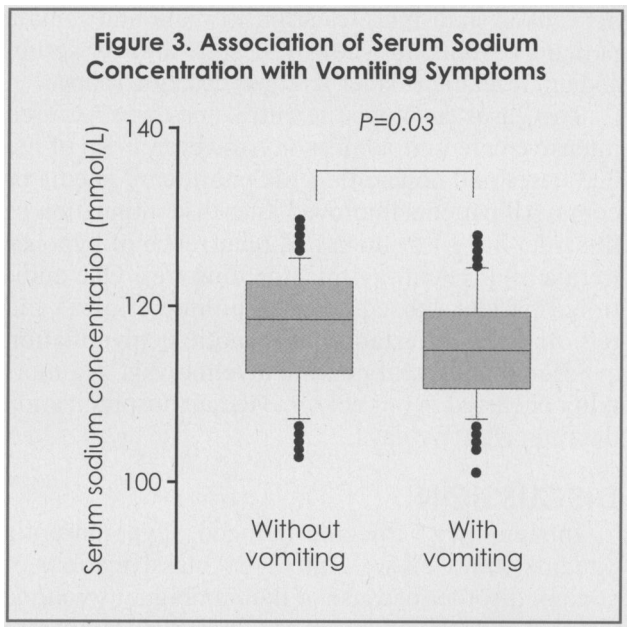
	Number (%)
Malaise/lethargy	109 (49%)
Dizzy spells	105 (47%)
Vomiting	77 (35%)
Confusion/obtundation	39 (17%)
Falls	37 (17%)
Headache	13 (6%)
Vertigo	13 (6%)
Seizures	2 (0.9%)
Noncardiogenic pulmonary edema	0
Coma	0

Previously postulated predisposition of female patients to brain damage from hyponatremia[10,11,14] could neither be confirmed nor refuted in our series because of the low event rate of seizures or coma. However, our finding of lower serum sodium concentration among female patients is speculated to be the effect of estrogen on thiazide binding in the kidney. Previous animal studies showed that estradiol enhanced thiazide-sensitive sodium cotransporter in the distal convoluted tubules,[15] which might therefore account for the greater magnitude of serum sodium fall among female thiazide-induced hyponatremic subjects. Potential limitations of this hypothesis-generating study, nevertheless, should be noted. First, the proposed effect of estrogen was not further examined, in the absence of patient data in terms of menopausal status and estrogen replacement therapy. In addition, the retrospective case series study design in the current setting without case-controls makes it difficult to infer unbiased causality.

In conclusion, it is clear from our study that hyponatremia from thiazide diuretics treatment may be easily missed if plasma electrolyte concentrations are not measured in patients with neurological manifestation. To summarize, it has been shown that symptoms from thiazide-induced hyponatremia primarily reflect osmotic water shift into brain cells rather than extracellular fluid volume depletion. These days,







when thiazide diuretics are advocated as the first-line antihypertensive therapy,[16,17] it is important to recognize the complication of thiazide-induced hyponatremia. The first step in the right direction is to be aware of such entity and clinical manifestations, and to further understand the pathophysiology with reference to the observed symptomatology.

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